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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/594,004	09/25/2006	Alfonso Romero	2294-0122PUS1	8959

2292 7590 11/26/2010

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EXAMINER	
FISHER, ABIGAIL L	
ART UNIT	PAPER NUMBER
1616	

NOTIFICATION DATE	DELIVERY MODE
11/26/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/594,004	ROMERO ET AL.	
	Examiner	Art Unit	
	ABIGAIL FISHER	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 September 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Receipt of Amendments/Remarks filed on September 10 2010 is acknowledged. Claims 1, 3-5, 7 and 11-15 were amended. Claims **1-15** are pending.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

New Objection Necessitated by the Amendments filed September 10 2010

Claim 1 is objected to because of the following informalities: the claim possesses an erroneous “3-5," between the m and a of the word “matrix". Appropriate correction is required.

Modified Rejections Based on amendments in the reply filed on September 10 2010

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Applicant Claims
2. Determining the scope and contents of the prior art.
3. Ascertaining the differences between the prior art and the claims at issue, and resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-5 and 7-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Maegerlein et al. (US PGPUB No. 20030153608, cited in the Office action mailed on 3/17/10) as evidenced by Azarmi et al. (Int. J. Pharmaceutics, 2002, cited in the Office action mailed on 3/17/10) in view of Tian et al. (WO 03072086).

Applicant Claims

The instant application claims prolonged-release compositions containing torasemide, a matrix-forming polymer and lactose.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

Maegerlein et al. exemplify a tablet (example 8) comprising formulation 1, calcium phosphate, croscarmelose (carboxymethylcellulose) (5 mg), Eudragit RL (8 mg), Aerosil 200 and magnesium stearate. Formulation 1 is present in 50 mg and of that 50 mg 20% is torasemide (as obtained from Table 1 for formulation 1). Therefore, as calculated by the examiner (since the total weight of the formulation of example 8 is 200 mg) the torasemide is present in 5%, Eudragit RL is present in 4% and crosscarmelose is present in 2.5%. The dosage forms are used for peroral administration (paragraph 0037). The preparations can additionally contain 0 to 94.5% by weight of customary pharmacologically acceptable excipients (paragraph 0027).

Ascertainment of the Difference Between Scope the Prior Art and the Claims *(MPEP §2141.012)*

While Maegerlein et al. teach that the preparations contain customary pharmacologically acceptable excipients, Maegerlein et al. does not teach the addition of lactose. However, this deficiency is cured by Tian et al.

Tian et al. is directed to pharmaceutical dosage forms with a tablet core. The tablet core comprises a release rate controlling additive. The drug may be held within a

hydrophobic polymer matrix so that it is gradually leached out of the matrix upon contact with body fluids (page 6, lines 19-21). It is taught that the tablet core may comprise another conventional tableting ingredients such as diluents. Examples of diluents include lactose and mannitol (page 7, lines 13-20).

Finding of Prima Facie Obviousness Rationale and Motivation (MPEP §2142-2143)

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to combine the teachings of Maegerlein et al. and Tian et al. and utilize lactose in the tablet formulation of Maegerlein et al. One of ordinary skill in the art would have been motivated to utilize lactose as Maegerlein et al. teach that customary pharmacologically acceptable excipients can be included and lactose is a customary excipient utilized in tablet formulation including those tablets which are controlled release.

Regarding the claimed prolonged release, as evidenced by Azarmi et al. Eudragit RL is known to be used in preparation of matrix tablets for oral sustained release (page 171, second paragraph).

Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over Maegerlein et al. as evidenced by Azarmi et al. in view of Tian et al. and in further view of Pankhania et al. (US Patent No. 5415871, cited in the Office action mailed on 3/17/10).

Applicant Claims

The instant application claims that the matrix-forming polymer is guar gum.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

The teachings of Maegerlein et al. are set forth above. Specifically, Maegerlein et al. exemplify a formulation comprising torasemide with an acrylic polymer. Other polymers taught include xanthan gum and galactomannan (guar gum) (paragraph 0022).

Ascertainment of the Difference Between Scope the Prior Art and the Claims *(MPEP §2141.012)*

Maegerlein et al. do not exemplify a formulation comprising guar gum. However, this deficiency is cured by Pankhania et al.

Pankhania et al. is directed to sustained release formulations. It is taught that polymers known for possessing sustained release properties include xanthan gum, guar gum, and acrylic resins. It is taught that one can be replaced for another (column 4, lines 8-24).

Finding of Prima Facie Obviousness Rationale and Motivation (MPEP §2142-2143)

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to combine the teachings of Maegerlein et al. and Pankhania et al. and replace the exemplify acrylic polymer with guar gum. One of ordinary skill in the art

would have been motivated to replace the exemplified acrylic polymer with guar gum as Maegerlein et al. teach that both are suitable and Pankhania et al. teach that both are known polymers for having sustained release properties. Therefore, one of ordinary skill in the art would have been motivated to replace the exemplified acrylic polymer with guar gum as both are taught by Pankhania et al. as functional equivalents in providing a sustained release.

Absent any evidence to the contrary, and based upon the teachings of the prior art, there would have been a reasonable expectation of success in practicing the instantly claimed invention. Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 1-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Berner et al. (US PGPUB No. 20030104052, cited in the Office action mailed on 3/17/10) in view of Kaplan (Drugs, 2000, cited in the Office action mailed on 3/17/10).

Applicant Claims

The instant application claims a prolonged release composition containing torasemide, a matrix-forming polymer and lactose.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

Berner et al. is directed to gastric retentive oral dosage form. The invention is a controlled release oral dosage form for the continuous, sustained administration of a pharmacologically active agent to the upper gastrointestinal tract (abstract). It is taught that the polymer used in the dosage form should not release the drug at too rapid a rate so as to result in drug overdose or rapid passage into and through the upper gastrointestinal tract (paragraph 0062). Suitable polymers taught include cellulosic polymers such as hydroxypropyl methylcellulose (paragraph 0066 and 085), acrylic acid and methacrylic acid polymers (paragraph 0067) and naturally occurring polymers such as guar gum (paragraph 0089). It is taught that the amount of polymer relative to the drug can vary depending on the drug release rate desired and the polymer, its molecular weight and excipient that may be present (paragraph 0096). Active agents include diuretic agent such as torsemide (paragraph 0119). The amount of drug ranges from 0.01 to 80% (paragraph 0133). Tablets prepared for oral administration will generally contain other materials such as binders, lubricants, disintegrants, fillers, etc. Suitable binders include starch and sugars such as lactose. Lubricants include magnesium stearate. Fillers include materials such as talc and mannitol (paragraph 0137).

Ascertainment of the Difference Between Scope the Prior Art and the Claims
(MPEP §2141.012)

While Berner et al. teach that a drug that can be administered is torasemide, Berner et al. do not exemplify a formulation comprising torasemide. However, this deficiency is cured by Kaplan.

Kaplan is directed to a review of diuretics as a basis of anti-hypertensive therapy. It is taught that to be effective the diuretic must have activity throughout the day when sodium is ingested in order to maintain a slight degree of contraction of the effective circulating fluid volume (paragraph bridging pages 21-22). Torasemide is recommended as a longer-acting diuretic (page 23, right column, firs complete paragraph). It is taught that long-acting formulations are preferred over short acting agent as there is better adherence with once-daily dosing, fewer tablets incur lower cost, control of hypertension is persistent and smooth rather than intermittent and protection is provided against whatever risk for sudden death, hear attach and stroke that is due to the abrupt increase blood pressure after arising from overnight sleep (page 23, right column, first paragraph of section 3).

Finding of Prima Facie Obviousness Rationale and Motivation (MPEP §2142-2143)

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to combine the teachings of Berner et al. and Kaplan and utilize torasemide as the active agent. One of ordinary skill in the art would have been motivated to utilize torasemide as Berner et al. teach it is a suitable drug and Kaplan teaches that torasemide is a recommended longer-acting diuretic as well as long-acting formulations are preferred over short-acting for many reasons including that control of hypertension is persistent and smooth and protection is provided. Therefore, one of ordinary skill in the art would have been motivated to utilize torasemide in the controlled

release formulation of Berner et al. for the benefits that long-acting formulations provide as taught by Kaplan.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to combine the teachings of Berner et al. and Kaplan and utilize polymers such as acrylic acid polymers, cellulose polymer like hydroxypropyl methylcellulose and guar gum as the polymer for providing sustained release. One of ordinary skill in the art would have been motivated to utilize these polymers as all are taught by Berner et al. as suitable for providing the sustained release of the active agent. It would have been obvious to one of ordinary skill in the art to try any of the swellable bioerodible polymers taught by Berner et al. as a person with ordinary skill has good reason to pursue known options within his or her technical grasp. **Note: MPEP 2141 [R-6]** *KSR International CO. v. Teleflex Inc.* 82 USPQ 2d 1385 (Supreme Court 2007).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to combine the teachings of Berner et al. and Kaplan and utilize conventional additives when formulating tablets for oral administration. One of ordinary skill in the art would have been motivated to add conventional additives such as lubricants like magnesium stearate, fillers such as talc or mannitol and binders such as lactose. Berner et al. teach that all of these additives for the formulation of tablets. Therefore, all of the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions and the combination would have yielded predictable results to

one of ordinary skill in the art at the time of the invention. **Note: MPEP 2141 [R-6]** *KSR International CO. v. Teleflex Inc.* 82 USPQ 2d 1385 (Supreme Court 2007).

Regarding the claimed amount of toresmide, Berner et al. teach an amount of drug that overlaps that instantly claimed. In the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a *prima facie* case of obviousness exists. **See MPEP 2144.05 [R-5]**

Regarding the claimed amount of polymer, Berner et al. that the amount of polymer relative to the drug can vary depending on the drug release rate desired and the polymer, its molecular weight and excipient that may be present. Therefore, the amount of polymer in a composition is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ and reasonably would expect success. It would have been customary for an artisan of ordinary skill to determine the optimal amount of each ingredient to add in order to best achieve the desired results. It would have been obvious to one of ordinary skill in the art to vary the amount of polymer in order to manipulate the release rate as taught by Berner et al. It would have been obvious to one of ordinary skill in the art at the time of the invention to engage in routine experimentation to determine optimal or workable ranges that produce expected results. Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. *In re Aller*, 220 F. 2d 454, 105 USPQ 233 (CCPA 1955).

Absent any evidence to the contrary, and based upon the teachings of the prior art, there would have been a reasonable expectation of success in practicing the instantly claimed invention. Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Response to Arguments/Declaration under Rule 132

Applicants argue that (1) Pankhania et al. states that the sustained release carrier comprises a major proportion of xanthan gum. While Pankhania et al. recite that guar gum can replace xanthan gum, there is no suggestion that the amount of guar gum would be different from the amount of xanthan gum used. Applicants argue that (2) lactose is a well known diluent which is not normally used in controlled release formulations. Applicants have shown that in comparison Sutril (which is an immediate release formulation), the instant formulations show prolonged release. Applicants point out that the lactose utilized in the experiments is above 45% and that the guar gum is less than 10% of the amount of lactose.

Applicants' arguments filed August 17 2010 and September 10 2010 have been fully considered but they are not persuasive.

Regarding applicants' first argument, the instant claims do not require a particular amount of xanthan gum. The exemplified acrylic polymers of Maegerlein et al. read on the instantly claimed amount of matrix-forming polymers. It appears by applicants' arguments that they agree that Pankhania teach that it would have been obvious to

substitute guar gum for xanthan gum. Therefore, the use of guar gum would have been obvious to one of ordinary skill in the art.

Regarding applicants' second argument, firstly, the instant claims do not require lactose and guar gum in any particular amount. Furthermore, even if they did, applicants have not demonstrated the unobviousness of these amounts. Additionally, while lactose may not be utilized to control the release of drugs, the use of lactose is conventionally utilized in controlled release formulations. Both Tian et al. and Berner et al. teach the use of lactose in controlled (prolonged) release formulations. The comparison data presented by applicants demonstrates that when compared to an immediate release compositions, the compounds of the instant invention show a prolonged release. However, this is not unobvious. One of ordinary skill in the art would expect a prolonged release by the presence of a polymeric matrix.

The declaration under 37 CFR 1.132 filed September 10 2010 is insufficient to overcome the rejection of claims 1-5 based upon Maegerlein et al., Pankhania et al. and Berner et al. as set forth in the last Office action because: the declaration presents the opinion that one of ordinary skill in the art would not choose to utilize lactose in prolonged release formulations. This is not found persuasive as both Tian et al. and Berner et al. teach the use of lactose in controlled release formulations. The data presented in the declaration demonstrates that when compared to an immediate release compositions, the compounds of the instant invention show a prolonged release.

However, this is not unobvious. One of ordinary skill in the art would expect a prolonged release by the presence of a polymeric matrix.

Therefore, the rejection is maintained since applicant has not provided any persuasive arguments to overcome the rejection.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ABIGAIL FISHER whose telephone number is (571)270-3502. The examiner can normally be reached on M-Th 9am-6pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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